Anticonvulsant drugs for management of pain: a systematic review

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Abstract

***Objective*—To determine effectiveness and adverse effects of anticonvulsant drugs in management of pain.**

***Design*—Systematic review of randomised controlled trials of anticonvulsants for acute, chronic, or cancer pain identified by using Medline, by hand searching, by searching reference lists, and by contacting investigators.**

***Subjects*—Between 1966 and February 1994, 37 reports were found; 20 reports, of four anticonvulsants, were eligible.**

***Main outcome measures*—Numbers needed to treat were calculated for effectiveness, adverse effects, and drug related withdrawal from study.**

***Results*—The only placebo controlled study in acute pain found no analgesic effect of sodium valproate. For treating trigeminal neuralgia, carbamazepine had a combined number needed to treat of 2·6 for effectiveness, 3·4 for adverse effects, and 24 for severe effects (withdrawal from study). For treating diabetic neuropathy, anticonvulsants had a combined number needed to treat of 2·5 for effectiveness, 3·1 for adverse effects, and 20 for severe effects. For migraine prophylaxis, anticonvulsants had a combined number needed to treat of 1·6 for effectiveness, 2·4 for adverse effects, and 39 for severe effects. Phenytoin had no effect on the irritable bowel syndrome, and carbamazepine had little effect on pain after stroke. Clonazepam was effective in one study for temporomandibular joint dysfunction. No study compared one anticonvulsant with another.**

***Conclusions*—Anticonvulsants were effective for trigeminal neuralgia and diabetic neuropathy and for migraine prophylaxis. Minor adverse effects occurred as often as benefit.**

Introduction

Anticonvulsant drugs have been used in pain management since the 1960s, soon after they were first used to revolutionise the management of epilepsy. The clinical impression is that they are useful for neuropathic pain, especially when the pain is lancinating or burning.[1] Although these disorders are not common (the incidence of trigeminal neuralgia is 4/100 000 a year[2]), they can be very disabling. Carbamazepine is one of few effective interventions for trigeminal neuralgia and is usually the drug of choice.[3] In Britain carbamazepine is licensed for paroxysmal pain of trigeminal neuralgia (up to 1600 mg daily). Phenytoin is also licensed for trigeminal neuralgia if carbamazepine is ineffective or if a patient cannot tolerate effective doses. When anticonvulsants are used as adjuvant drugs in other pain syndromes valproate is often preferred to carbamazepine because it may be better tolerated.[4] Anticonvulsants are also prescribed in combination with antidepressants, as in the treatment of post-herpetic neuralgia.[5] In Britain no anticonvulsant is licensed for treating any pain other than trigeminal neuralgia.

Serious side effects have been reported with anticonvulsant drugs, including deaths from haematological reactions.[6] The commonest adverse effects are impaired mental and motor function, which may limit clinical use, particularly in elderly people.[6-8]

The purpose of this review was to evaluate the effectiveness of anticonvulsant drugs as analgesics in order to provide evidence based recommendations for clinical practice and to identify an agenda for clinical research. We used the "number needed to treat" method[9] to produce clinically interpretable measures of benefit, minor harm, and major harm.

Methods

SELECTION OF REPORTS

We included reports if they were randomised controlled trials of the analgesic effects of anticonvulsant drugs. We excluded studies if they were not randomised; were studies of experimental pain, case reports, or clinical observations; or were studies of anticonvulsants used to treat pain produced by other drugs.

Reports were identified by several methods. We conducted a Medline search (SilverPlatter 3.0, 3.1, and 3.11) from 1966 to February 1994 with a search strategy designed to identify the maximum number of randomised or double blind reports by means of a combination of text words, "wild cards," and MeSH terms.[10] This search strategy was narrowed to include specific anticonvulsant drugs. We hand searched 40 medical journals, chosen from the 50 with the highest number of reports in Medline, and nine specialist journals that were either not on that list or not indexed.[11] Our search covered volumes published between 1950 and 1990. We identified additional reports from the reference list of the retrieved papers. A letter was sent to the first author for further information on their published report (method of randomisation, double blinding, outcome measures, and dropouts) and to ask if they knew of any other studies which met our inclusion criteria, done either by them or by other investigators.

Eligibility was determined by reading each report identified by the search. We scored the reports independently for quality using a three item scale[11] and then met to agree a consensus score for each report. Studies that were described as randomised were given one point, and a further point was given if the method of randomisation was described and was appropriate (such as use of random number tables). If randomisation was inappropriate (such as alternate allocation) one point was deducted and the report was excluded. Studies that were described as double blind were given one point. A further point was given if blinding was described and was appropriate (such as matched placebos), and one point was deducted if blinding was inappropriate. Reports that described the number and reasons for withdrawals were given one point. The

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BMJ 1995;311:1047-52

maximum score was 5 and the minimum for an included report was 1.

INFORMATION GATHERED

From each report we gathered information about the pain condition and the number of patients studied; the anticonvulsant drug used and the treatment regimen; study design (placebo control or control with active treatment); duration of the study and follow up; outcome measures and results; and minor and major (drug related withdrawal from study) adverse effects. Reports often used several different measures of pain. The prior definition of a clinically relevant outcome was greater than 50% pain relief. We extracted information about improvement in binary form for analysis, and we used a hierarchy of measures: the number of patients free of pain at the end of the study; complete, excellent, or very good response; or the number of patients who improved. No weighting was used between these different indices.

STATISTICAL ANALYSIS

Odds ratios and 95% confidence intervals were calculated with a fixed effects model. We calculated numbers needed to treat and 95% confidence intervals[9] for effectiveness, for adverse effects and for drug related withdrawal from study, both for the individual reports and for combined single treatment or control arms.

Results

We identified 37 reports (all published), 34 from Medline and three from reference lists. Of these, 17 were excluded and one report[12] was a duplicate publication (table I). The remaining 20 randomised controlled trials were eligible for our study. Four anticonvulsant drugs were used: carbamazepine in 10 of the trials, phenytoin in five, clonazepam in three, and sodium valproate in two. The pain conditions investigated were chronic non-malignant pain (in 17 trials), cancer pain (one trial), postoperative pain (one trial), and acute herpes zoster (one trial). Tables II and III give details of the eligible placebo controlled trials and active treatment controlled trials respectively. The median quality score for the placebo controlled studies was 3 (range 2-5) and for the active treatment controlled studies was 2 (range 1-4).

We requested data from 19 authors. Five replied, but only one (Leijon) was able to supply information relevant to this review.

ACUTE PAIN

The only placebo controlled study of treating acute pain compared sodium valproate 15 mg/kg with the non-steroidal anti-inflammatory drug ketoprofen (2 mg/kg) and placebo, all given intravenously over 20 minutes.[38] Ketoprofen produced a significant fall in pain intensity compared with placebo, but valproate did not (table II). In a comparison of carbamazepine and prednisolone for managing acute herpes zoster, the 20 patients given prednisolone reported less pain and faster skin healing (3·7 weeks *v* 5·3 weeks) than the 20 given carbamazepine 400 mg/day, and 13 of the patients given carbamazepine still had pain after two months compared with three of those given prednisolone (table III).[42]

CHRONIC PAIN

Trigeminal neuralgia

Of the 12 placebo controlled studies of treating chronic pain, three were for trigeminal neuralgia, all with carbamazepine (table II).[22-31] In a crossover trial 19 out of 27 patients had a complete or very good response after five days' treatment with carbamazepine (titrated to a maximum dose of 1 g/day), compared with none after placebo.[30] Again with a crossover design and dose titration (to a maximum dose of 2·4 g/day), 15 of the 20 patients given initial carbamazepine had a good or excellent response after 14 days' treatment compared with six of the 24 patients given initial placebo.[31] The extent to which the pain was relieved may be gauged from the third study.[29] With doses ranging from 400 mg/day to 800 mg/day given for periods of two weeks, the mean fall in maximum pain intensity was 58% with carbamazepine compared with 26% with placebo. The effectiveness odds ratios of two of the three studies, and the combined ratio, showed carbamazepine to be more effective than placebo. The number needed to treat for effectiveness compared with placebo was 2·6, that for minor adverse effects was 3·4, and that for drug related withdrawal from the study was 24 (table IV).

Three active treatment controlled studies compared carbamazepine with tizanidine (α_2 adrenergic agonist),[43] tocainide (antiarrhythmic drug),[44] and pimozide (antipsychotic drug)[45] (table III). Carbamazepine produced better results than tizanidine; there was no significant difference in the tocainide study; and pimozide produced better results than carbamazepine.

Diabetic neuropathy

Two placebo controlled studies of treating diabetic neuropathy (one with carbamazepine[32] and one with phenytoin[36]) found that treatment with anticonvulsant resulted in 30-50% more patients improving after two weeks than did placebo. A third study comparing treatment with phenytoin for 23 weeks with placebo found no difference in mean pain intensity.[37] For the two studies with dichotomous data, the combined effectiveness odds ratio showed a significant effect for anticonvulsant compared with placebo. The number needed to treat for effectiveness compared with

TABLE I—*Reports of anticonvulsant drugs used for pain relief that were excluded from analysis*

Report	Anticonvulsant	Pain condition	Reason for exclusion
Arieff *et al*[13]	Carbamazepine	Neuralgias	Not randomised controlled trial
Farago[14]	Carbamazepine	Trigeminal neuralgia	Not randomised controlled trial
Fromm *et al*[15]	Carbamazepine	Trigeminal neuralgia	Not randomised controlled trial
Goncikowska[16]	Carbamazepine	Horton's headache	Not randomised controlled trial
Hatta *et al*[17]	Phenytoin	Suxamethonium induced myalgia	Suxamethonium induced myalgia
Holmes *et al*[18]	Flunarizine	Not applicable	Review, not randomised controlled trial
Hopkins[19]	Carbamazepine	Drug interaction	Not randomised controlled trial, drug interaction
Kienast *et al*[20]	Carbamazepine	Trigeminal neuralgia	Not randomised controlled trial
Kienast *et al*[12]	Carbamazepine	Trigeminal neuralgia	Not randomised controlled trial, dual publication
Matthew *et al*[21]	Sodium valproate	Chronic headache	Not randomised controlled trial
Naidu *et al*[22]	Phenytoin	Rheumatoid arthritis	Not randomised controlled trial
Rasmussen *et al*[23]	Carbamazepine	Facial pain	Not randomised controlled trial, single blind
Schaffler *et al*[24]	(3-(4-Hydroxypipridyl)6-(2'chlorophenyl)-pyridazine)	Experimental pain in volunteers	Experimental pain
Sharav *et al*[25]	Carbamazepine	Trigeminal neuralgia	Case report, not randomised controlled trial
Shibasaki *et al*[26]	Carbamazepine	Fabry's disease	Case report, not randomised controlled trial
Westerholm[27]	Carbamazepine	Facial pain	Not randomised controlled trial
Young *et al*[28]	Clonazepam	Diabetic neuropathy	Not randomised controlled trial

TABLE II—*Reports of anticonvulsant drugs used for pain relief that were included in analysis: trials with placebo control*

Report	Condition (No of patients)	Design; duration; follow up*	Outcome measures	Dosing regimen	Analgesic outcome	Withdrawals; adverse effects	Quality score†
			Carbamazepine				
Campbell *et al*[29]	Trigeminal neuralgia (77)	Multicentre crossover; eight weeks (four two week periods, two each on carbamazepine (and placebo); no follow up	Pain severity, paroxysms, triggers	100 mg four times daily to 200 mg three times daily (one centre) or 200 mg (four times daily) (two centres)	Mean maximum possible pain intensity fell 58% with carbamazepine, 26% with placebo; paroxysms and triggers also significantly reduced	Seven withdrawals (one rash, others logistic); 50% had one or more adverse effect with carbamazepine, 26% with placebo; giddiness 30%, drowsiness 15%	5
Killian *et al*[30]	Trigeminal neuralgia (30), postherpetic neuralgia (6), other chronic neuralgias (6). 36/42 studied double blind (24/32 trigeminal neuralgia)	Crossover; 10 days (two five day periods); open follow up, range two weeks to 36 months	Pain relief	Dose titration 400 mg to 1 g daily	19/27 trigeminal neuralgia complete or very good response; placebo responses "minimal or absent in all cases"	3/30 trigeminal neuralgia withdrawn (rash, leukopenia, abnormal liver function); adverse effects in 23/36 studied double blind; 17 giddiness, 16 drowsiness	4
Nicol[31]	64 with facial pain recruited, 54 with trigeminal neuralgia; results presented on 44 trigeminal neuralgia only "due to insufficient follow up"	Partial crossover (successful first treatment stayed on that treatment); 20 had carbamazepine only, seven had placebo only, 17 had placebo then carbamazepine; follow up 46 months	Global rating (pain intensity and adverse effects)	Dose titration 100 mg to 2·4 g daily	15/20 taking carbamazepine from start had good or excellent response; 12/17 switched from placebo to carbamazepine; 6/7 given placebo had good or excellent response	2/37 given carbamazepine withdrawn (one rash, one itch); 4/37 with carbamazepine died (of other causes); 10/37 drowsiness, 7/37 staggering gait	3
Rull *et al*[32]	Diabetic neuropathy (30)	Crossover; six weeks (three two week periods); no follow up	Pain intensity	Dose titration 200 mg to 600 mg daily	28/30 given carbamazepine improved *v* 19/30 given placebo; 0/30 given carbamazepine worsened *v* 11/30 given placebo	Three withdrawals (two carbamazepine adverse effects, one logistic); 16/30 somnolence, 12/30 dizziness	4
Rompel *et al*[33]	Migraine prophylaxis (48)	Crossover; 12 weeks (two six week periods); no follow up	No of migraines, global rating	One tablet three times daily‡	38/45 given carbamazepine improved *v* 13/4 given placebo; 30 migraines in 45 given carbamazepine, 186 in 48 given placebo	Three withdrawals (one adverse effects with carbamazepine, two logistic); 30/45 had adverse effects with carbamazepine (23 vertigo or dizziness), 11/48 with placebo	4
Leijon *et al*[34]	Central pain after stroke (15)	Crossover; 14 weeks (three four week periods with two one week washouts); no follow up	Daily pain intensity, post-treatment global rating	Stepped increase to final day (day 18) 800 mg daily; amitriptyline 75 mg daily at day 6	Daily rating; with amitriptyline significantly lower pain intensity than with placebo on 3/3 weeks tested, and carbamazepine on 1/3 weeks tested. Global: 10/15 given amitriptyline improved, 5/14 given carbamazepine, 1/15 given placebo	No withdrawals; 14/15 with amitriptyline and carbamazepine had adverse effects, 1/15 with placebo; four carbamazepine patients had dose reduced	4
			Phenytoin				
Greenbaum *et al*[35]	Irritable bowel (14)	Crossover; 20 weeks (four week run in, six weeks treatment, four week wash out, six weeks treatment); no follow up	Bowel movements, pain episodes	Fixed 300 mg/day	No significant differences between phenytoin and placebo; no quantitative data available	Two withdrawals, neither drug related; no report of adverse effects	4
Chadda *et al*[36]	Diabetic neuropathy (40)	Crossover; five weeks (two two week periods, one week washout); no follow up	Pain intensity, paraesthesiae	Fixed 300 mg/day	28/38 given phenytoin had at least moderate improvement *v* 10/38 given placebo	Two withdrawals ("did not report back"); 4/38 giddiness with phenytoin	2
Saudek *et al*[37]	Diabetic polyneuropathy (12)	Crossover; 46 weeks (2×23 weeks); no follow up	Pain intensity	One capsule three times daily titrated *v* plasma concentration	No significant differences between phenytoin and placebo: mean pain score 7·2 mm for phenytoin plasma concentration <5 mg/l (placebo 8 mm), and 19·1 *v* 20 mm for >5 mg/l	Two drug related withdrawals with phenytoin, none with placebo; with phenytoin significant increase in plasma glucose and four times more reports of adverse effects (16 *v* 4)	2
			Sodium valproate				
Martin *et al*[38]	Acute postoperative pain (39)	Parallel group; 140 minutes	Pain intensity	15 mg/kg sodium valproate *v* placebo *v* 2 mg/kg ketoprofen, each given intravenously over 20 minutes	No significant difference between valproate and placebo. Ketoprofen significantly reduced pain intensity (80 to 25 mm mean) compared with valproate and placebo (80 to 60 mm)	None reported	2
Hering *et al*[39]	Migraine prophylaxis (32)	Crossover; 10 weeks (two week run in, two eight week periods); no follow up	No of attacks, duration, pain intensity	Fixed 400 mg twice daily	Significant reduction in mean No of attacks (15 to 8), duration, and pain intensity (24 to 15) with valproate. Valproate effective in 25/29	Three withdrawals (one valproate advese effects, two placebo); with valproate 2/29 dyspepsia, 2/29 nausea, 2/29 weariness	3
			Clonazepam				
Stensrud *et al*[40]	Migraine prophylaxis (38)	Crossover; 16 weeks (four week run in, three four week periods; placebo *v* high and low doses of clonazepam); followed up on 2 mg/day for four weeks	Headache days	Fixed 1 mg and 2 mg daily	Significant reduction in headache days between 1 mg (50%) and 2 mg (37%) and run in period, but not for placebo (8%)	Four withdrawals (three lethargy with 1 mg clonazepam, other unclear); 23/38 drowsy with clonazepam, 10 dizzy	3
Harkins *et al*[41]	Temporomandibular joint dysfunction (myofascial pain) (20)	Parallel group; 60 days; open follow up	Pain intensity on palpation, global pain	Dose titration 0·25 mg to 1 mg daily (mean 0·375 mg)	Significantly lower mean pain intensity and global pain at 30 days (*v* baseline) with clonazepam compared with placebo (about 40% change with clonazepam, 20% with placebo)	6/10 given clonazepam withdrew (one at week 1 (headache), five at 30 days because pain improved); 7/10 given placebo withdrew at 30 days because not improved; 3/10 given clonazepam drowsy	3

*Studies were single centre unless stated otherwise. †Maximum score=5, minimum score=0. ‡Actual dose not specified.

placebo was 2·5, that for adverse effects was 3·1, and that for drug related withdrawal from the study was 20 (table IV).

There were no eligible active treatment control studies of diabetic neuropathy.

Migraine prophylaxis

Of three placebo controlled studies of treating migraine prophylaxis, with three different anticonvulsants, two showed greater effect with the anticonvulsant than with placebo (table II). Six weeks of treatment with carbamazepine 3 tablets/day led to improvement in 38 out of 45 patients compared with 13 of the 48 given placebo.[33] Sodium valproate 800 mg/day for eight weeks produced significant reduction in the number of migraines, in their duration, and in the pain intensity; it was effective in 25 out of 29 patients.[39] The third study was of 1 or 2 mg of clonazepam daily for 60 days and found no significant difference between clonazepam and placebo.[40] For the two studies with dichotomous data, the combined effectiveness odds ratio showed a significant effect for anticonvulsant compared with placebo; the number needed to treat for effectiveness compared with placebo was 1·6, that for adverse effects was 2·4, and that for drug related withdrawal from the study was 39 (table IV).

There were no eligible active treatment control studies of migraine prophylaxis.

Other pain syndromes

Placebo controlled studies (table II)—Phenytoin 300 mg/day for six weeks had no effect in the one study of the irritable bowel syndrome.[35] Four weeks of carbamazepine treatment at a final dose of 800 mg/day was judged to have improved central pain after stroke in five out of 14 patients, compared with 10 out of 15 patients given amitriptyline 75 mg and one out of 15 patients given placebo.[34] In a 60 day study of clonazepam (mean daily dose 0·375 mg) for temporomandibular joint dysfunction, analysis at 30 days showed significantly lower pain intensity scores with the anticonvulsant compared with placebo.[41]

Active treatment controlled studies (table III)—A 24 week comparison of phenytoin and intramuscular gold showed that gold gave significantly better relief of pain and morning stiffness from rheumatoid arthritis.[46] Phenytoin 200 mg/day was compared with buprenorphine alone and a combination of buprenorphine and phenytoin (100 mg/day) for treating cancer pain; all three regimens produced good or moderate relief in more than 60% of patients.[47] In a comparison of a combination of carbamazepine and clomipramine with

TABLE III—*Reports of anticonvulsant drugs used for pain relief that were included in analysis: trials with active treatment control*

Report	Condition (No of patients)	Design; duration; comparator; follow up*	Outcome measures	Dosing regimen	Analgesic outcome	Withdrawals; adverse effects	Quality score†
			Carbamazepine				
Keczlees *et al*[42]	Acute herpes zoster (40)	Parallel group; four weeks; prednisolone; clinic follow up until no pain (maximum > 1 year)	Pain, skin healing, incidence of post-herpetic neuralgia (> 2 months)	4×100 mg day carbamazepine; prednisolone 40 mg/day for 10 days then reduced to 0 mg over next three weeks	Skin healing significantly faster with prednisolone; post-herpetic neuralgia in 13/20 carbamazepine patients, 3/20 prednisolone patients	Not reported	1
Vilming *et al*[43]	Trigeminal neuralgia (12)	Parallel group; three weeks tizandine; no follow up	Pain intensity, pain relief, global	Carbamazepine titrated 3×300 mg/day; tizanidine to 3×6 mg/day	4/6 carbamazepine patients rated treatment as very good, 1/5 tizandine patients	Three withdrawals with tizanidine, one not drug related, two because of intolerable pain	3
Lindstrom *et al*[44]	Trigeminal neuralgia (12)	Crossover; four weeks (two two week periods); tocainide; no follow up	Severity, frequency, and duration of attacks= trigeminal neuralgia score	Maximum tolerated dose of carbamazepine; tocainide about 20 mg/kg/day in three divided doses	Tocainide and carbamazepine produced similar improvement compared with placebo—no significant difference between the active treatments	Tocainide 1/10 nausea, 1/10 paraesthesiae, 1/10 rash (withdrawn)	2
Lechin *et al*[45]	Trigeminal neuralgia (68)	Multicentre (four) crossover; 24 weeks (four week placebo run in then two eight week periods with four week wash out); pimozide; open follow up with pimozide	Trigeminal neuralgia symptom score	Step titration carbamazepine 300-1200 mg daily; pimozide 4-12 mg daily in two divided doses	Pimozide lowered symptom score by 78% from baseline compared with 50% with carbamazepine	68 recruited, 59 randomised, 11 excluded from analysis (10 protocol deviation, one did not return); 40/48 adverse effects with pimozide, 21/48 with carbamazepine	4
			Phenytoin				
Richards *et al*[46]	Rheumatoid arthritis (60)	Parallel group, single blind; 24 weeks; intramuscular gold; no follow up	Pain, morning stiffness	Step titration phenytoin 100 mg/day increased by 50 mg/week to effect or adverse effect; gold 10 mg test dose then 50 mg/week, then, if effective, 50 mg/2 weeks	Mean pain score improvement of 40/100 with gold, 12/100 with phenytoin	Six withdrawals with phenytoin, (two no effect, one rash, one sleep difficulty, one lethargy, one unrelated death); six withdrawals with gold (two rash, one no effect, three proteinuria)	2
Yajnik *et al*[47]	Cancer pain (75)	Parallel group four weeks; buprenorphine, combination of buprenorphine+ phenytoin; no follow up	Pain intensity, pain relief	Phenytoin 2×100 mg/day; buprenorphine 2×0·2 mg sublingual/day, 0·1 mg sublingual buprenorphine+ phenytoin 50 mg twice a day	Good or moderate relief in 21/25 buprenorphine only, in 18/25 phenytoin only, and in 22/25 combination patients	13/25 affected with buprenorphine only, 2/25 with phenytoin only, 5/25 with combination	2
			Combinations				
Gerson *et al*[48]	Post-herpetic neuralgia (29)	Parallel group; eight weeks carbamazepine+ clomipramine (16) *v* transcutaneous nerve stimulation (13); no follow up	Pain intensity, activity, mood	Carbamazepine 150 mg-1 g/day; clomipramine 10-75 mg/day, nerve stimulation 15 min/week for four weeks	Mean improvement 43/100 mm with drug combination, 0·2 with nerve stimulation	Seven withdrawals with drug treatment, four (no effect) crossed (successfully) to nerve stimulation, 10 withdrawals with nerve stimulation; eight crossed to drug treatment (three successfully)	2

*Studies were single centre unless stated otherwise. †Maximum score=5, minimum score=0.

TABLE IV—*Placebo controlled reports of effect of anticonvulsants on chronic pain: number needed to treat for effectiveness, adverse effects, and drug related withdrawal from study*

Report	Effectiveness				Adverse effects				Drug related withdrawal from study			
	No of patients improved with active treatment	No of patients improved with placebo	Odds ratio (95% confidence interval)	No needed to treat (95% confidence interval)	No of patients with adverse effects with active treatment	No of patients with adverse effects with placebo	Odds ratio (95% confidence interval)	No needed to treat (95% confidence interval)	No of patients withdrawn from active treatment	No of patients withdrawn from placebo	Odds ratio (95% confidence interval)	No needed to treat (95% confidence interval)
Trigeminal neuralgia												
Campbell *et al*[29]	144/268*	35/190*	4·4 (3 to 6·4)	2·8 (2·3 to 3·7)	38/77	20/77	2·7 (1·4 to 5·1)	4·3 (2·6 to 11·7)	1/77	0/77	7·4 (0·1 to 372·4)	77 (26·1 to ∞)
Killian *et al*[30]	19/27	0/27	20·6 (6·8 to 62·3)	1·4 (1·14 to 1·88)	23/36	0/30	16 (5·8 to 43·9)	1·6 (1·3 to 2·1)	3/30	0/30	8 (0·8 to 79·3)	10 (4·8 to ∞)
Nicol *et al*[31]	15/20	6/7	0·5 (0·1 to 4)	−9·3 (4·7 to ∞)	10/37	0/7	4·5 (0·7 to 30·1)	3·7 (2·4 to 7·9)	2/37	0/7	3·4 (0·1 to 156·3)	18·5 (7·9 to ∞)
Combined	178/315	41/224	4·9 (3·4 to 6·9)	2·6 (2·2 to 3·3)	71/150	20/114	3·7 (2·2 to 6·2)	3·4 (2·5 to 5·2)	6/114	0/114	6·2 (1·2 to 31·7)	24 (13·5 to 110·8)
Diabetic neuropathy												
Rutt *et al*[32]	28/30	19/30	5·7 (1·7 to 19·2)	3·3 (2 to 9·4)	16/30	0/30	14·6 (4·7 to 45·5)	1·9 (1·4 to 2·8)	2/30	0/30	7·7 (0·5 to 126·6)	15 (6·4 to ∞)
Chadda *et al*[26]	28/38	10/38	6·5 (2·7 to 15·9)	2·1 (1·5 to 3·6)	4/38	0/38	8 (1·1 to 59·4)	9·5 (4·9 to 130)	0/38	0/38	NA	NA
Saudele *et al*[27]	ND	ND	ND	ND	10/12	4/12	7·2 (1·5 to 35·3)	2 (1·2 to 6·3)	2/12	0/12	8 (0·5 to 136)	6 (2·6 to ∞)
Combined	56/68	29/68	5·4 (2·7 to 10·7)	2·5 (1·8 to 4)	30/80	4/80	6·9 (3·2 to 14·6)	3·1 (2·3 to 4·8)	4/80	0/80	7·7 (1·1 to 55·7)	20 (10·2 to 446)
Migraine prophylaxis												
Rompel *et al*[33]	38/45	13/48	9·9 (4·4 to 22·2)	1·7 (1·4 to 2·4)	30/45	11/48	5·8 (2·6 to 13·1)	2·3 (1·6 to 3·9)	1/48	0/48	7·4 (0·1 to 372·4)	48 (16·3 to ∞)
Hering *et al*[34]	25/29	4/29	17·2 (6·2 to 47·7)	1·4 (1·1 to 1·8)	6/29	2/29	3·1 (0·7 to 13·7)	7·3 (3·2 to ∞)	1/32	2/32	0·5 (0·1 to 5)	NA
Stensrud *et al*[35]	ND	ND	ND	ND	23/38	0/38	17 (6·4 to 44·8)	1·7 (1·3 to 2·2)	3/38	0/38	7·8 (0·8 to 77·4)	12·7 (6·1 to ∞)
Combined	63/74	17/77	6·1 (3·5 to 10·5)	1·6 (1·3 to 2)	59/112	13/115	6·7 (3·8 to 11·7)	2·4 (1·9 to 3·3)	5/118	2/118	2·4 (0·5 to 10·8)	39·3 (14·6 to ∞)
Other pain syndromes												
Leijon *et al*[36]	5/14	1/15	5·5 (0·9 to 32·3)	3·4 (1·7 to 105)	14/15	1/15	28·5 (7 to 116·5)	1·2 (1 to 1·5)	0/15	0/15	NA	NA
Greenbaum *et al*[25]	ND	ND	ND	ND	NA	NA	NA	NA	0/12	0/12	NA	NA
Harleus *et al*[41]	ND	ND	ND	ND	4/10	0/10	10·8 (1·3 to 91)	2·5 (1·4 to 10·4)	1/10	0/10	7·4 (0·1 to 372.4)	10 (3·5 to ∞)

*77 Patients assessed on multiple crossover.
NA=not applicable or not available.
ND=no dichotomous data available.

transcutaneous electrical nerve stimulation for treating post-herpetic neuralgia, drug treatment produced improvement in nine out of 16 patients while nerve stimulation produced improvement in three out of 13 patients.[48]

ADVERSE EFFECTS AND DRUG RELATED WITHDRAWAL FROM STUDY

In the placebo controlled studies there were 16 drug related withdrawals from anticonvulsant treatment compared with two from placebo (table IV). Where adverse effects were reported the incidence was 25-50% in each study. Drowsiness, dizziness, and disturbance in gait were the common problems.

Discussion

Although randomised controlled trials are the optimum method of assessing health care technologies and interventions,[49] buttressed by double blinding when outcome measures are subjective,[50-52] many interventions are time honoured rather than supported by trials. On whom does the burden of proof then fall?[53] The aim of our study was to review the effectiveness and safety of anticonvulsant drugs in the management of pain, restricting the review to reports of randomised controlled trials.

We used the number needed to treat approach because most of the data was in dichotomous form, which lends itself to this analysis, and because the number needed to treat is more readily clinically interpretable than, for example, effect sizes. The number needed to treat was calculated for minor and major adverse effects as well as for effectiveness because adverse effects are important for clinical decision making. This approach may be useful for reviews of other long established interventions. The older the report, the more likely it was to present simple binary data, such as improved versus not improved. More recent reports which restricted data presentation to mean data for treatment and control were not accessible to the method.

EFFECTIVENESS OF ANTICONVULSANT DRUGS

Anticonvulsants were ineffective in the one report of postoperative pain[38] and in the one of acute herpes zoster.[42] There is no logic in using anticonvulsants to manage acute nociceptive pain when there are other (effective) remedies.

The overall pattern of a number needed to treat for effectiveness of about 2·5, for adverse effects of about 3, and for drug related withdrawal from the study of 20-40 was surprisingly similar for the three pain syndromes that were subject to more than one trial (table IV).

Trigeminal neuralgia—Medical students are often taught that a positive response to carbamazepine is diagnostic for trigeminal neuralgia. However, if only one out of every two patients responds to the treatment, this statement needs to be qualified. One caveat is that the study populations may have included patients who had other interventions, such as nerve blocks, and the number needed to treat for effectiveness may be more impressive when trigeminal neuralgia is treated with carbamazepine in the initial stages. The statement that "approximately 70% of patients will have significant pain relief"[3] would seem to be about right.

Diabetic neuropathy is perceived as a model for other neuropathic pain syndromes, and results from diabetic neuropathy are often extrapolated to other syndromes. The studies reviewed here gave conflicting results, with a negative result in the longest study (46 weeks) balanced by two studies with positive results. The number needed to treat for effectiveness was the same as that for adverse effects. The usual clinical decision is between antidepressants and anticonvulsants as first

Key messages

- Anticonvulsants are used widely to control trigeminal neuralgia and other chronic neuropathic pains
- To evaluate the effectiveness of these drugs, we conducted a systematic review of all randomised controlled trials reported between 1966 and February 1994
- Only 20 trials were eligible for inclusion, and three pain syndromes were subject to more than one trial: trigeminal neuralgia, diabetic neuropathy, and migraine prophylaxis.
- Overall number needed to treat to produce benefit (improved pain scores) was about 2·5, for minor adverse effects it was about 3, and for severe adverse effects it was 20-30
- Anticonvulsants do have an analgesic effect, although at similar risk of minor adverse effects

line treatment. A direct comparison of antidepressant and anticonvulsant activities is available from the study of pain after stroke, in which the number needed to treat for effectiveness was 1·7 for amitriptyline and was 3·4 for carbamazepine, with the same number needed to treat for adverse effects and study withdrawal.[34]

Migraine prophylaxis—The three placebo controlled randomised controlled trials showed anticonvulsants to be effective, but recent advances in migraine management may reduce the impact of these results.

CONCLUSION

This review shows that there is a need for high quality studies of the relative effectiveness of different anticonvulsants in treating chronic pain syndromes and for comparisons of antidepressants with anticonvulsants. The usefulness of such primary studies would be greatly increased by improvements in the quality of reporting. Investigators presenting data as means for treatment and control should also consider the (simple) presentation of binary data, for example the number of patients with more than 50% pain relief.

We thank Clare Abbott and Jo Riordan for helping to locate the reports. We are also very grateful to the authors of the original reports who took the trouble to reply to our correspondence and those who provided us with original data: S Vilming, F Lechin, G Leijon, D Greenbaum, and S Yajnik.

Funding: Supported by a grant from Oxford Regional Health Authority and Pain Research Funds.

Conflict of interest: None.

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(Accepted 26 June 1995)

ONE HUNDRED YEARS AGO

WHAT IS A HABITUAL DRUNKARD?

The daily journals report the presentation of a petition to the House of Lords, praying that any person who has been twice convicted of drunkenness within two years in the same licensing district shall be defined to be a habitual drunkard, and that any licensed dealer serving or harbouring him after due notice shall be liable to penalties and forfeiture of licence. So severe a measure will, we feel assured, never be enacted by any civilised Legislature. In existing legislation three convictions within six months—as in South Australia—constitute an inebriate a "habitual drunkard;" but twice in two years is utterly irrational. The late Government's Inebriates Bill proposed three convictions within twelve months, but the too drastic character of this definition would have been altered if the Bill had gone on. The object of the petition is excellent, though the operation of the Bill could be effectual only in small communities, where the inhabitants would know such cases. (*BMJ* 1895;ii:96.)